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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Microwave assisted synthesis of novel pyrimidine derivatives and investigation of their analgesic and ulcerogenic activity

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Abstract A novel series of 6-bromo-3-(2-morpholino methyl amino)-6-substituted phenyl pyrimidine-4-yl-2H-chromone-2-one **(6aM–6jM)** and 3-(2-((piperidine-1-yl) methyl amino)-6- substituted phenylpyrimidin-4-yl)-6-bromo-2H-chromone-2-one **(6aP–6jP)** have been synthesized from 3-(2-amino-6-pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (**5a–5j**) which were synthesized from 3-acetyl-6-bromo-2H-chromen-2-one (**3**). The reactions were carried out by conventional and microwave method. The salient feature of microwave method are rapid reaction rate, cleaner reaction condition, and enhancement in chemical yield compared to conventional method, the structures of the synthesized compounds were characterized by I.R., ^{1}H NMR, ^{13}C NMR, Mass spectroscopic techniques. All the compounds screened at a dose of 20 mg/kg body weight by in vivo analgesic activity. Among all the synthesized compounds, compound **6aP**, **6aM**, **6cM**, **6iM**, and **6jM** showed significant analgesic activity and compounds **6cM** and **6iM** showed highly significant activity against the standard drug Diclofenac sodium using acetic acid-induced writhing model. Among all the synthesized compounds which show potent analgesic activity such as **6aP**, **6aM**, **6cM**, **6iM**, and **6jM** were further evaluated for acute- ulcerogenic activity. Among all compound **6cM** and **6iM** was found to be most promising analgesic agent devoid of ulcerogenic effects.

Keywords Pyrimidines · Knoevenagel reaction · Claisen-Schmidt condensation · Microwave method · Analgesic activity

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Introduction

The investigation of compounds able to treat both acute and chronic pain is challenging in pharmaceutical research (Williams *et al.,* 1999), pain is in fact a very important problem present in 90% of diseases, from the simple back pain to pain associated with different forms of cancer. The classical therapies for pain treatment are mainly the non-steroidal-anti-inflammatory drugs (NSAIDs) and opiates, whose lead compounds, acetylsalicylic acid and morphine, respectively, were isolated in nineteenth century (Dardonville *et al.,* 2003).

NSAIDs show side effects such as gastrointestinal irritation and lesions, renal toxicity, and inhibition of platelet aggregation, while the use of opioids is limited to severe pain because of adverse secondary reactions as respiratory depression, dependence, sedation, and constipation (Giovannoni *et al.,* 2003; Walsh, 1990). Hence there is always a

need of new drugs which have improved analgesic activity and less adverse effects.

Nitrogen containing heterocyclic compound such as pyrimidine is a promising structural moiety for drug designing. Pyrimidine derivatives form a component in a number of useful drugs and are associated with many biological, pharmaceutical, and therapeutically activities (Patel *et al.,* 2003). Condensed pyrimidine derivatives have been reported as anti-microbial (Desai *et al.,* 2006), analgesic, anti-viral, anti-inflammatory (Amr *et al.,* 2007), anti-HIV (Fujiwara *et al.,* 2008), anti-tubercular (Ballell *et al.,* 2007), anti-tumour (Wagner *et al.,* 2008), anti-neoplastic (Cordeu *et al.,* 2007), anti-malarial (Dawood *et al.,* 2006), diuretic (Ukrainets *et al.,* 2008), cardiovascular agents (Kurono *et al.,* 1987). Pyrimidine compounds are also used as hypnotic drugs for the nervous system (Wang *et al.,* 2004), calcium-sensing receptor antagonists (Yang *et al.,* 2009) and also for antagonists of the human A_{2A} adenosine receptor (Gillespie *et al.,* 2009). Like pyrimidine, coumarin also exhibits diverse biological properties (Kulkarni *et al.,* 2006; Keri *et al.,* 2010).

It was envisaged that these two active pharmacophores, if linked together would generate novel molecular templates which are likely to exhibit interesting biological properties in animal models. The above-cited applications prompted us to synthesize a series of new compounds reported in this article.

During our synthetic studies, it was observed that the synthesis of 6-Bromo-3-(2-morpholino methyl amino)-6-substituted phenyl pyrimidine-4-yl-2H-chromone-2-one **(6aM–6jM)** and 3-(2-((piperidine-1-yl)methyl amino)-6-substituted phenylpyrimidin-4-yl)-7-bromo-2H-chromone-2-one **(6aP–6jP)** from 3-acetyl-6-bromo-2H-chrome required reaction time of 8–10 h while the yields were poor. Therefore, it was felt worthwhile to study these reactions under microwave irradiation with aim of increasing the yield and decreasing the reaction time as well as less solvent requirement. In addition, microwave irradiated synthesis provided an easy and quicker work up and there by cleaner reaction.

The compounds were screened for their in vivo analgesic and ulcerogenic activity. Thus, we have created new avenues to explore the potent heterocyclic moieties for the pharmacological activities in medicinal chemistry.

Experimental

Chemistry

All reagents and solvents were used as obtained by the supplier (Fisher Scientific India, Central Drug House (P) Ltd. India, HiMedia Laboratories India). The melting points (m. p.) were determined by open capillary method and were uncorrected. I.R. Spectra (KBr) have done on FTIR Spectrophotometer (Shimadzu FTIR 84005, 4000–400 cm^{-1}). The elemental analysis was carried out using Heraus CHN rapid analyzer. ^{1}H NMR and ^{13}C NMR spectra recorded on a JEOL AL300 FTNMR 300 MHz spectrometer in $CDCl_3$ using TMS as an internal standard, with ^{1}H resonance frequency of 300 MHz and ^{13}C resonance frequency of 75 MHz. Chemical shift values were expressed in δ ppm. The homogeneity of the compounds was described by TLC on alumina silica gel using solvent system "Toluene:Ethylacetate:Formic acid" (5:4:1) detected by iodine vapours. The reaction was carried out in a LG domestic microwave oven (model no.MC-7148MS). The activity was performed at M.I.E.T., Meerut, India. The physical data of all these compounds were summarized in Table 1.

*Synthesis of 3-acetyl-6-bromo-2H-chromen-2-one (**3**)*

Conventional method A reagent 5-bromo salicyldehyde **(1)** (0.02 mol) and ethyl acetoacetate **(2)** (0.03 mol) was

Table 1 Physical parameters of compounds (**6aP–6jP** and **6aM–6jM**)

Compounds	Reaction time		Yield (%)[b]	
	Conventional	MW (min)	Conventional	MW (h)
6aP	8.00–9.00	4.50	50.4	82.1
6bP	8.00–9.00	5.00	60.7	80.4
6cP	9.00–10.00	5.00	60.5	75.9
6dP	9.00–10.00	4.30	65.3	83.6
6eP	8.00–9.00	4.40	50.7	74.4
6fP	8.30–9.00	5.00	60.5	77.0
6gP	9.00–9.30	5.00	65.3	81.1
6hP	8.00–9.00	4.40	65.8	73.4
6iP	8.00–8.30	4.50	60.9	85.4
6jP	8.00–9.00	5.00	55.6	86.1
6aM	9.00–10.00	4.10	55.4	77.4
6bM	8.00–9.00	5.00	60.9	72.8
6cM	9.00–10.00	4.50	60.7	79.4
6dM	9.00–10.00	5.00	65.1	74.7
6eM	9.00–10.00	4.40	50.9	75.0
6fM	9.00–10.00	5.00	60.5	78.4
6gM	9.00–10.00	5.00	65.3	77.4
6hM	8.30–9.00	5.00	65.5	71.9
6iM	9.00–10.00	4.50	60.3	73.3
6jM	9.00–10.00	4.50	55.1	76.7

[a] Products were characterized by IR, NMR, MS, and elemental analysis

[b] Synthesized yields

[c] m. p. are uncorrected

dissolved in ethanol and reaction followed in round-bottom flask. In this reaction few drops of piperidine were added as a catalyst and refluxed for 2–3 h. After completion of reaction, the content was poured on crushed ice. The solid was obtained after filtration, dried and recrystallized by ethanol.

Microwave method A reagent 5-bromo salicyldehyde **(1)** (0.02 mol), ethyl acetoacetate **(2)** (0.03 mol) and few drops of piperidine were taken in a conical flask, covered with a glass funnel. A petridish containing few ice cubes was kept on funnel to prevent excess evaporation of solvent. The reaction mixture was exposed to microwave irradiation for 2 min at 160 W. A beaker containing water was also kept in oven to serve as a heat sink, to monitor the progress of reaction, a TLC was run after every minute of microwave irradiation using "Benzene:Acetone" (9:1) solvent system. After completion of reaction, the content was poured on crushed ice. The solid separated was filtered, dried and recrystallized from ethanol. The formation of compound **(3)** can be explained on the basis of "Knoevenagel reaction". m. p. 115–117°C; IR (KBr, cm^{-1}): 1735.81 and 1674.10 (C=O), 1550.66 (C=C), 1230.50 (aryl ethers, C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 2.58 (s, 3H, CH_3), 7.25–7.98 (m, 4H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 35.50, 120.9, 123.8, 126.6, 127.3, 130.5, 132.5, 139.8, 155.7, 163, 200.6; Anal. calcd for $C_{11}H_7BrO_3$ (267.08): C, 70.21; H, 4.29.

*Synthesis of 6-bromo-3-((E)-3-(substituted)-acryloyl)-2H-chromen-2-one (**4a–4j**)*

Conventional method Equimolar quantities of different substituted benzaldehyde and 3-acetyl-6-bromo-2H-chromen-2-one **(3)** in the presence of absolute ethanol and piperidine few drop were refluxed for 8–10 h. After completion of reaction mixture was concentrated and poured on to crushed ice. The solid obtained were filtered, dried, and recrystallized from ethanol to get pure product. The formation of compounds (**4a–4j**) can be explained on the basis of "Claisen-Schmidt condensation".

Microwave method Equimolar quantities of 3-acetyl-6-bromo-2H-chromen-2-one **(3)** and different substituted benzaldehydes in absolute ethanol using piperidine as a catalyst were taken in a conical flask, covered with a glass funnel. A petridish containing few ice cubes was kept on funnel to prevent excess evaporation of solvent. The reaction mixture was exposed to microwave irradiation for 8 min at 320 W. A beaker containing water was also kept in oven to serve as a heat sink, to monitor the progress of reaction, a TLC was run after every minute of microwave irradiation using "Benzene:Acetone" (9:1) solvent system. After completion of reaction, the solution mixture was concentrated and poured on to crushed ice. The compound so obtained were filtered at pump, dried, and recrystallized from ethanol to get pure crystalline solid. The formation of compounds (**4a–4j**) can be explained on the basis of "Claisen-Schmidt condensation".

*Synthesis of 6-bromo-3-((E)-3-(2-chlorophenyl)-acryloyl)-2H-chromen-2-one (**4a**)* The compound **(4a)** obtained by reacting of compound **(3)** with 2-Chlorobenzaldehyde. m. p.: 162–165°C; Rf. value (benzene:acetone; 9:1): 0.73; IR (KBr, cm^{-1}): 1724.24 and 1662.52 (C=O), 1556.45 (C=C), 1184.21 (C–O–C); ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 6.02 (d, 1H, CH), 7.11–7.93 (m, 8H, Ar–H), 8.03 (d, 1H, CH); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 120.3, 124.2, 125.3, 125.9, 129.1, 129.9, 130, 131.9, 132.5, 133, 138.9, 142.6, 143.9, 145.2, 147.6, 157.8, 159.6, 180.5; Anal. calcd for $C_{18}H_{10}BrClO_3$ (389.63): C, 69.58; H, 3.57.

*Synthesis of 6-bromo-3-((E)-3-(3-chlorophenyl)-acryloyl)-2H-chromen-2-one (**4b**)* The compound **(4b)** obtained by reacting of compound **(3)** with 3-Chlorobenzaldehyde. m. p.: 165–167°C; Rf. value (benzene:acetone; 9:1) :0.75; IR (KBr, cm^{-1}): 1728.10 and 1685.67 (C=O), 1558.38 (C=C), 1107.06 (C–O–C); ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 7.03 (d, 1H, CH), 7.15–8.02 (m, 8H, Ar–H), 8.66 (d, 1H, CH); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 120.9, 122.9, 124.6, 125.9, 127.6, 128.9, 130.2, 130.9, 131.5, 132.7, 133, 135.7, 138.9, 144.9, 148.2, 158.3, 160.5, 178.6; Anal. calcd for $C_{18}H_{10}BrClO_3$ (389.63): C, 69.58; H, 3.57.

*Synthesis of 6-bromo-3-((E)-3-(4-chlorophenyl)-acryloyl)-2H-chromen-2-one (**4c**)* The compound **(4c)** obtained by reacting of compound **(3)** with 4-Chlorobenzaldehyde. m. p.: 156–158°C; Rf. Value (benzene:acetone; 9:1): 0.71; IR (KBr, cm^{-1}): 1728.10 and 1685.67 (C=O), 1558.38 (C=C), 1107.06 (C–O–C). ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 6.36 (d, 1H, CH), 6.90 (d, 1H, CH), 7.02–8.48 (m, 8H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 120.5, 123.4, 124.6, 127.5, 128.4, 128.6, 128.9, 130.5, 130.9, 131.5, 131.7, 132.6, 132.9, 144.4, 145.6, 157.2, 158.6, 182.9; Anal. calcd for $C_{18}H_{10}BrClO_3$ (389.63): C, 69.58; H, 3.57.

*Synthesis of 6-bromo-3-((E)-3-(2-bromophenyl)-acryloyl)-2H-chromen-2-one (**4d**)* The compound **(4d)** obtained by reacting of compound **(3)** with 2-Bromobenzaldehyde. m. p.: 190–192°C; Rf. value (benzene:acetone; 9:1): 0.77; IR (KBr, cm^{-1}): 1724.24 and 1683.74 (C=O), 1556.43 (C=C), 1184.21 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 6.86 (d, 1H, CH), 7.02–7.93 (m, 8H, Ar–H), 8.00 (d, 1H, CH); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 120.1, 120.9, 121.5, 121.9, 124.6, 125.6, 127.6, 127.9, 128.6, 128.9, 129.4, 129.9,

130.9, 145.6, 149.3, 159.6, 161.9, 178.5; MS, [M^+], *m/z* 433 (100%), [$M^+ +2$], *m/z* 435 (25%), [$M^+ +4$], *m/z* 437 (2%); Anal. calcd for $C_{18}H_{10}Br_2O_3$ (434.08): C, 60.87; H, 3.12.

*Synthesis of 6-bromo-3-((E)-3-(3-bromophenyl)-acryloyl)-2H-chromen-2-one (**4e**)* The compound **(4e)** obtained by reacting of compound **(3)** with 3-bromobenzaldehyde. m. p.: 185–187°C; Rf. value (benzene: acetone; 9: 1): 0.76; IR (KBr, cm^{-1}): 1728.10 and 1685.67 (C=O), 1558.38 (C=C), 1107.06 (C–O–C); ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 7.08 (d, 1H, CH), 7.11–7.99 (m, 8H, Ar–H), 8.05 (d, 1H, CH); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 1209, 123.5, 124.6, 125.9, 126.9, 127.8, 128.7, 129, 129.4, 130, 131.5, 131.6, 134.6, 140, 147.3, 150.6, 158.3, 179.2; Anal. calcd for $C_{18}H_{10}Br_2O_3$ (434.08): C, 60.87; H, 3.12.

*Synthesis of 6-bromo-3-((E)-3-(4-bromophenyl)-acryloyl)-2H-chromen-2-one (**4f**)* The compound **(4f)** obtained by reacting of compound **(3)** with 4-bromobenzaldehyde. m. p.: 185–188°C; Rf. value (benzene:acetone; 9:1): 0.69; IR (KBr, cm^{-1}): 1739.67 and 1677.95 (C=O), 1558.38 (C=C), 1107.06 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 7.03 (d, 1H, CH), 7.11–7.94 (m, 8H, Ar–H), 8.23 (d, 1H, CH); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 121.9, 122.3, 123.6, 124.6, 125.3, 125.9, 128.6, 128.9, 129.5, 129.9, 130.5, 132.3, 135, 145.6, 150, 160.3, 164.2, 165.1, 180; Anal. calcd for $C_{18}H_{10}Br_2O_3$ (434.08): C, 60.87; H, 3.12.

*Synthesis of 6-bromo-3-((E)-3-(2-methoxyphenyl)-acryloyl)-2H-chromen-2-one (**4g**)* The compound **(4g)** obtained by reacting of compound **(3)** with 2-Methoxybenzaldehyde. m. p.: 180–182°C; Rf. value (benzene:acetone; 9:1): 0.64; IR (KBr, cm^{-1}): 1728.10 (C=O), 16085.67 (C=C), 1164.92 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 3.56 (s, 3H, CH_3), 6.86 (d, 1H, CH), 7.02–7.96 (m, 8H, Ar–H), 8.09 (d, 1H, CH); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 62.7, 113.5, 118.6, 120.3, 121.6, 123.6, 125.9, 127.6, 128, 128.9, 129, 129.9, 143.9, 150, 155.6, 160.3, 163.5, 163.9, 179; Anal. calcd for $C_{19}H_{13}BrO_4$ (385.21): C, 74.50; H, 4.61.

*Synthesis of 6-bromo-3-((E)-3-(3-methoxyphenyl)-acryloyl)-2H-chromen-2-one (**4h**)* The compound **(4h)** obtained by reacting of compound **(3)** with 3-Methoxybenzaldehyde. m. p.: 173–175°C; Rf. value (benzene:acetone; 9:1): 0.69; IR (KBr, cm^{-1}): 1735.81 (C=O), 1674.10 (C=C), 1137.92 (C–O–C); ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 3.90 (s, 3H, CH_3), 6.98 (d, 1H, Ar–H), 7.00–7.85 (m, 8H, Ar–H), 8.10 (d, 1H, CH); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 63.2, 112.5, 118.2, 120.9, 122.9, 122.5, 126.9, 127.9, 128, 128.6, 129.3, 129.9, 142.6, 150.3, 154.6, 160.8, 163.6, 165.9, 182.3; MS, [M^+], *m/z* 384 (100%), [$M^+ +2$], *m/z* 386 (20%), [$M^+ +4$], *m/z* 388 (1.5%); Anal. calcd for $C_{19}H_{13}BrO_4$ (385.21): C, 74.50; H, 4.61. Found: C, 74.45; H, 4.56.

*Synthesis of 6-bromo-3-((E)-3-(2, 4-dichlorophenyl)-acryloyl)-2H-chromen-2-one (**4i**)* The compound **(4i)** obtained by reacting of compound **(3)** with 2,4-dichlorobenzaldehyde. m. p.: 175–177°C; Rf. value (benzene:acetone; 9:1): 0.71; IR (KBr, cm^{-1}): 1739.67 (C=O), 1677.95 (C=C), 1103.21 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 6.98 (s, 1H, CH), 7.00–7.85 (m, 6H, Ar–H), 7.93 (s, 1H, CH), 8.43 (s, 1H, CH); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 121.9, 122.9, 123.2, 125.9, 126.5, 127.9, 128, 128.6, 129.3, 129.9, 132.5, 136.5, 136.9, 150.3, 152.6, 165.9, 166.3, 182.3; Anal. calcd for $C_{18}H_9BrCl_2O_3$ (424.27): C, 62.63; H, 2.92.

*Synthesis of 6-bromo-3-((E)-3-(2, 6-dichlorophenyl)-acryloyl)-2H-chromen-2-one (**4j**)* The compound **(4j)** obtained by reacting of compound **(3)** with 2,6-dichlorobenzaldehyde. m. p.: 180–183°C; Rf. value (benzene:acetone; 9:1): 0.79; IR (KBr, cm^{-1}): 1739.67 (C=O), 1677.95 (C=C), 1161.07 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 6.87 (s, 1H, CH), 7.00–7.95 (m, 6H, Ar–H), 8.0 (s, 1H, CH), 8.43 (s, 1H, CH); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 121.1, 122.2, 123.9, 125, 126.9, 127.5, 128, 128.9, 129.3, 130.9, 132.4, 136.9, 138.9, 151.9, 155.5, 167.9, 169.5, 185.8; Anal. calcd for $C_{18}H_9BrCl_2O_3$ (424.27): C, 62.63; H, 2.92.

*Synthesis of 3-(2-amino-6-(2-chlorophenyl)-pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (**5a–5j**)*

Conventional method The reaction were carried out between compounds **(4a–4j)** (0.01 mol) and guanidine HCl (0.02 mol) in presence of ethanol and refluxed for 8–10 h. After completion of reaction content was evaporated to dryness and washed with water repeatedly and recrystallized from ethanol.

Microwave method The reaction were carried out between compounds **(4a–4j)** (0.01 mol) and guanidine HCl (0.02 mol) in ethanol were taken in a conical flask, covered with a glass funnel. A petridish containing few ice cubes was kept on funnel to prevent excess evaporation of solvent. The reaction mixture was exposed to microwave irradiation for 6 min at 480 W.A beaker containing water was also kept in oven to serve as a heat sink, to monitor the progress of reaction, a TLC was run after every minute of microwave irradiation using "Benzene:Acetone" (9:1) solvent system. After completion of reaction, the solution mixture was concentrated and poured on to crushed ice.

The compound so obtained were filtered at pump, dried and recrystallized from ethanol to get pure crystalline solid.

*Synthesis of 3-(2-amino-6-(2-chlorophenyl)-pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (**5a**)*

The compound **(5a)** was obtained by reacting **(4a)** with guanidine HCl. m. p.: 162–165°C; Rf. value (benzene:acetone; 9:1): 0.62; IR (KBr, cm^{-1}): 3431.55 (N–H), 1709.55 (C=O), 1612.04 (C=N), 1535.90 (C=C), 1129.17(C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 4.256 (s, 2H, NH_2), 6.85–7.72 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 110.1, 124.2, 125.3, 128.6, 129.1, 129.9, 130, 131.9, 132.5, 135.5, 138.9, 142.6, 143.9, 145.2, 147.6, 157.8, 165.6, 168.5, 170.5; Anal. calcd for $C_{19}H_{11}BrClN_3O_2$ (428.67): C, 65.24; H, 3.46; N, 12.01.

*Synthesis of 3-(2-amino-6-(3-chlorophenyl)-pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (**5b**)*

The compound **(5b)** was obtained by reacting **(4b)** with guanidine HCl. m. p.: 165–167°C; Rf. value (benzene:acetone; 9:1): 0.74; IR (KBr, cm^{-1})': 3174.61 (N–H), 1654.81 (C=O), 1596.95 (C=N), 1546.80 (C=C), 1234.36 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 4.25 (s, 2H, NH_2), 6.92–7.36 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 109.2, 122.9, 124.6, 125.9, 127.6, 128.9, 130.2, 131.5, 132.7, 133, 135.7, 138.9, 144.9, 148.2, 158.3, 160.5, 161.4, 163.4, 170.9; Anal. calcd for $C_{19}H_{11}BrClN_3O_2$ (428.67): C, 65.24; H, 3.46; N, 12.01.

*Synthesis of 3-(2-amino-6-(4-chlorophenyl)-pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (**5c**)*

The compound **(5c)** was obtained by reacting **(4c)** with guanidine HCl. m. p.: 156–158°C; Rf. value (benzene:acetone; 9:1): 0.70; IR (KBr, cm^{-1}): 3340.48 (N–H), 1685.67 (C=O), 1593.09 (C=N), 1542.95 (C=N), 1238.61 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 4.25 (s, 2H, NH_2), 7.02–7.50 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 110.5, 123.4, 124.6, 127.5, 128.4, 128.6, 128.9, 130.5, 130.9, 131.5, 131.7, 132.6, 132.9, 144.4, 145.6, 157.2, 158.6, 160.9, 163.7; Anal. calcd for $C_{19}H_{11}BrClN_3O_2$ (428.67): C, 65.24; H, 3.46; N, 12.01.

*Synthesis of 3-(2-amino-6-(2-bromophenyl)-pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (**5d**)*

The compound **(5d)** was obtained by reacting **(4d)** with guanidine HCl. m. p.: 190–192°C; Rf. value (benzene:acetone; 9:1): 0.75; IR (KBr, cm^{-1}): 3355.91 (N–H), 1654.81 (C=O), 1600.81 (C=N), 1542.95 (C=N), 1238.21 (C–O–C); ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 4.96 (s, 2H, NH_2), 7.25–7.63 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 107.9, 120.5, 121.5, 121.9, 124.6, 125.6, 127.6, 127.9, 128.6, 128.9, 129.4, 129.9, 130.9, 145.6, 149.3, 159.6, 161.9, 162.8, 164.9; Anal. calcd for $C_{19}H_{11}Br_2N_3O_2$ (473.12): C, 57.89; H, 3.07; N, 10.66.

*Synthesis of 3-(2-amino-6-(3-bromophenyl)-pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (**5e**)*

The compound **(5e)** was obtained by reacting **(4e)** with guanidine HCl. m. p.: 185–187°C; Rf. value (benzene:acetone; 9:1): 0.72; IR (KBr, cm^{-1}): 3355.91 (N–H), 1654.81 (C=O), 1542.95 (C=N), 1477.37 (C=N), 1269.07 (C–O–C); ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 4.27 (s, 2H, NH_2), 6.93–7.63 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm):109.9, 123.5, 124.6, 125.9, 126.9, 127.8, 128.7, 129, 129.4, 130, 131.5, 131.6, 134.6, 140, 147.3, 150.6, 158.3, 160, 165.8; Anal. Calcd for $C_{19}H_{11}Br_2N_3O_2$ (473.12): C, 57.89; H, 3.07; N, 10.66.

*Synthesis of 3-(2-amino-6-(4-bromophenyl)-pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (**5f**)*

The compound **(5f)** was obtained by reacting **(4f)** with guanidine HCl. m. p.: 185–188°C; Rf. value (benzene:acetone; 9:1): 0.68; IR (KBr, cm^{-1}): 3417.63 (N–H), 1666.38 (C=O), 1604.66 (C=N), 1477.37 (C=N), 1234.36 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 4.16 (s, 2H, NH_2), 6.90–7.73 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 109.3, 122.3, 123.6, 124.6, 125.3, 125.9, 128.6, 128.9, 129.5, 129.9, 130.5, 132.3, 135, 145.6, 150, 160.3, 164.2, 165.1, 167; Anal. calcd for $C_{19}H_{11}Br_2N_3O_2$ (473.12): C, 57.89; H, 3.07; N, 10.66.

*Synthesis of 3-(2-amino-6-(2-methoxyphenyl)-pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (**5g**)*

The compound **(5g)** was obtained by reacting **(4g)** with guanidine HCl. m. p.: 177–179°C; Rf. value (benzene:acetone; 9:1): 0.67; IR (KBr, cm^{-1}): 3382.91 (N–H), 1670.24 (C=O), 1600.81 (C=N), 1477.37 (C=N), 1245.93 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 3.87 (s, 3H, CH_3), 4.25 (s, 2H, NH_2), 6.92–8.00 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 63.7, 106.3, 113.5, 118.6, 120.3, 121.6, 123.6, 125.9, 127.6, 128, 128.9, 129, 129.9, 143.9, 150, 155.6, 160.3, 163.5, 163.9, 166.3; Anal. calcd for $C_{20}H_{14}BrN_3O_3$ (424.25): C, 69.56; H, 4.38; N, 12.17.

*Synthesis of 3-(2-amino-6-(3-methoxyphenyl)-pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (**5h**)*

The compound **(5h)** was obtained by reacting **(4h)** with guanidine HCl. m. p.: 173–177°C; Rf. value (benzene:

acetone;9:1): 0.65; IR (KBr, cm^{-1}): 3367.48 (N–H), 1666.38 (C=O), 1600.81 (C=N), 1577.66 (C=N), 1265.22 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 3.81 (s, 3H, CH_3), 4.04(s, 2H, NH_2), 6.86–7.25 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 63.2, 106.6, 112.5, 118.2, 120.9, 122.9, 122.5, 126.9, 127.9, 128, 128.6, 129.3, 129.9, 142.6, 150.3, 154.6, 160.8, 163.6, 165.9, 167.5; Anal. calcd for $C_{20}H_{14}BrN_3O_3$ (424.25): C, 69.56; H, 4.38; N, 12.17.

*Synthesis of 3-(2-amino-6-(2, 4-dichlorophenyl)-pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (**5i**)*

The compound **(5i)** was obtained by reacting **(4i)** with guanidine HCl. m. p.: 175–177°C; Rf. value (benzene:acetone; 9:1): 0.78; IR (KBr, cm^{-1}): 3417.63 (N–H), 1677.95 (C=O), 1589.23 (C=N), 1473.51 (C=N), 1234.36 (C–O–C); ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 4.06 (s, 2H, NH_2), 7.0–7.40 (m, 7H, Ar–H), 7.95 (s, 1H, CH); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 105.4, 120.5, 121.9, 123.5, 124.6, 127.9, 128.5, 128.9, 129.9, 130, 132.6, 133.6, 135.6, 138.7 145.6, 150.3, 154.9, 160.8, 165.9; Anal. calcd for $C_{19}H_{10}BrCl_2N_3O_2$ (463.11): C, 59.39; H, 2.89; N, 10.94.

*Synthesis of 3-(2-amino-6-(2, 6-dichlorophenyl)-pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (**5j**)*

The compound **(5j)** was obtained by reacting **(4j)** with guanidine HCl. m. p.: 180–183°C; Rf. value (benzene:acetone; 9:1): 0.70; IR (KBr, cm^{-1}): 3425.34 (N–H), 1604.66 (C=O), 1600.81 (C=N), 1577.66 (C=N), 1265.22 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 4.03 (s, 2H, NH_2), 7.10–7.60 (m, 7H, Ar–H), 7.95 (s, 1H, CH); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 104.5, 120.9, 121.9, 123.9, 124.8, 126.7, 127.5, 129.1, 129.9, 130.2, 132.9, 133.7, 135, 140.7, 150.6, 150.9, 154.9, 157.03, 165.9; Anal. calcd for $C_{19}H_{10}BrCl_2N_3O_2$ (463.11): C, 59.39; H, 2.89; N, 10.94.

*Synthesis of 6-Bromo-3-(6-(substituted)-2-(morpholinomethylamino) pyrimidin-4-yl)-2H-chromen-2-one (**6aM–6jM**)*

Conventional method A mixture of compounds **(5a–5j)** (0.01 mol) and morpholine (0.01 mol) and formaldehyde (0.02) was refluxed in ethanol for 6–10 h. The reaction mixture was reduced to half of it's volume and poured on crushed ice. The product so obtained was washed with water repeatedly, dried and recrystallized from ethanol. The formation of compounds (**6aM–6jM**) can be explained on the basis of "Mannich reaction".

Microwave method A mixture of compounds **(5a–5j)** (0.01 mol) and morpholine (0.01 mol) and formaldehyde (0.02) was refluxed in ethanol were taken in a conical flask, covered with a glass funnel. A petridish containing few ice cubes was kept on funnel to prevent excess evaporation of solvent. The reaction mixture was exposed to microwave irradiation for 5 min at 480 W. A beaker containing water was also kept in oven to serve as a heat sink, to monitor the progress of reaction, a TLC was run after every minute of microwave irradiation using "Benzene:Acetone" (9:1) solvent system. After completion of reaction, the solution mixture was concentrated and poured on to crushed ice. The compound so obtained were filtered at pump, dried, and recrystallized from ethanol to get pure crystalline solid.

*Synthesis of 6-bromo-3-(6-(2-Chlorophenyl)-2-(morpholinomethylamino) pyrimidin-4-yl)-2H-chromen-2-one (**6aM**)*

It was obtained by reacting **(5a)** with morpholine and formaldehyde. m. p.: 176–178°C; Rf. value (benzene:acetone; 9:1) :0.76; IR (KBr, cm^{-1}): 3280.30 (N–H), 1706.90 (C=O), 1605.16 (C=N), 1542.35 (C=C),1130.80 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 4.08(s, 1H, NH),2.37(t, 4H, 2 × CH_2), 3.67(t, 4H, 2 × CH_2),6.87–7.73 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 51.3, 66.7, 72.6, 107.4, 121.4, 122.8, 124.9, 127.6, 128.6, 128.8, 129.2, 129.6, 130.2, 130.4, 132.5, 146.2, 152.6, 160.4, 161.8, 162.1, 165.9; MS *m/z*: 527.0, 410.9,303.1(100%), 217.0, 151.1; Anal.calcd for $C_{24}H_{20}BrClN_4O_3$(526.04): C, 54.62; H, 3.82; N, 10.62.

*Synthesis of 6-bromo-3-(6-(3-Chlorophenyl)-2-(morpholinomethylamino) pyrimidin-4-yl)-2H-chromen-2-one (**6bM**)*

It was obtained by reacting **(5b)** with morpholine and formaldehyde. m. p.: 175–177°C; Rf. value (benzene:acetone; 9:1) :0.74; IR (KBr, cm^{-1}): 3285.12 (N–H), 1708.88 (C=O), 16054.26 (C=N), 1542.30 (C=C), 1131.50 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 4.09(s, 1H, NH), 2.38(t, 4H, 2 × CH_2), 3.66 (t, 4H, 2 × CH_2), 6.89–7.74 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 51.2, 66.6, 72.5, 107.4, 121.5, 122.8, 125.7, 127.6,128.8, 129.3, 129.4, 129.5, 130.8, 134.9, 146.3, 152.5, 160.3, 161.9, 162.2, 165.8; Anal. calcd for $C_{24}H_{20}BrClN_4O_3$ (526.04): C, 54.62; H, 3.82; N, 10.62.

*Synthesis of 6-bromo-3-(6-(4-Chlorophenyl)-2-(morpholinomethylamino) pyrimidin-4-yl)-2H-chromen-2-one (**6cM**)*

The compound **(6cM)** was obtained by reacting **(5c)** with morpholine & formaldehyde. m. p.: 177–179°C; Rf. value (benzene:acetone; 9:1): 0.66; IR (KBr, cm^{-1}): 3287.10 (N–H), 1710.06 (C=O), 1604.16 (C=N), 1541.45

(C=C), 1132.45 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 4.04(s, 1H, NH), 2.36(t, 4H, 2 × CH_2), 3.68 (t, 4H, 2 × CH_2), 6.86–7.73 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 51.2, 66.7, 72.5, 107.4, 121.5, 122.8, 122.9, 124.9, 128.5, 128.7, 129.5, 131.4, 134.5, 146.3, 152.6, 160.4, 161.8, 162.2, 165.9; MS *m/z*: 527.8, 304.0, 222.93, 204.0, 163.0; Anal. calcd for $C_{24}H_{20}BrClN_4O_3$ (526.04): C, 54.62; H, 3.82; N, 10.62.

*Synthesis of 6-bromo-3-(6-(2-bromophenyl)-2-(morpholinomethylamino) pyrimidin-4-yl)-2H-chromen-2-one (**6dM**)*

It was obtained by reacting **(5d)** with morpholine and formaldehyde. m. p.: 180–182°C; Rf. value (benzene:acetone; 9:1): 0.73; IR (KBr, cm^{-1}): 3286.20 (N–H), 1707.80 (C=O), 16053.12 (C=N), 1540.38 (C=C), 1129.70 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 4.02(s, 1H, NH), 2.35(t, 4H, 2 × CH_2), 3.65(t, 4H, 2 × CH_2), 6.85–7.73 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 51.3, 66.6, 72.5, 107.4, 120.5, 121.4, 122.8, 124.9, 128.4, 128.5, 129.2, 129.5, 131.2, 132.4, 139.7, 152.5, 161.8, 162.2, 165.9; MS *m/z*: 517.0, 347.0, 206.9, 156.2,100.2(100%); Anal. calcd for $C_{24}H_{20}Br_2N_4O_3$ (569.99): C, 50.37; H, 3.52; N, 9.79.

*Synthesis of 6-Bromo-3-(6-(3-bromophenyl)-2-(morpholinomethylamino) pyrimidin-4-yl)-2H-chromen-2-one (**6eM**)*

It was obtained by reacting **(5e)** with morpholine and formaldehyde. m. p.: 175–178°C; Rf. value (benzene:acetone; 9:1): 0.72; IR (KBr, cm^{-1}) : 3284.40 (N–H), 1705.80 (C=O), 1606.10 (C=N), 1543.30 (C=C), 1131.25 (C–O–C); ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 4.03(s, 1H, NH), 2.36 (t, 4H, 2 × CH_2), 3.66(t, 4H, 2 × CH_2), 6.86–7.71 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 51.3, 66.4, 72.5, 107.4, 120.5, 121.5, 122.8, 123.7, 124.9, 126.7, 128.6, 128.6, 129.2, 129.5, 131.7, 133.2, 135.5, 146.2, 152.5, 160.2, 161.8, 165.9; Anal. calcd for $C_{24}H_{20}Br_2N_4O_3$ (569.99): C, 50.37; H, 3.52; N, 9.79.

*Synthesis of 6-Bromo-3-(6-(4-bromophenyl)-2-(morpholinomethylamino) pyrimidin-4-yl)-2H-chromen-2-one (**6fM**)*

It was obtained by reacting **(5f)** with morpholine and formaldehyde. m. p.: 178–180°C; Rf. value (benzene:acetone; 9:1) : 0.68; IR (KBr, cm^{-1}): 3282.15 (N–H), 1707.60 (C=O), 1605.20 (C=N), 1544.40 (C=C), 1128.90 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 4.05(s, 1H, NH), 2.34(t, 4H, 2 × CH_2), 3.63 (t, 4H, 2 × CH_2), 6.84–7.71 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 51.3, 66.6, 72.5, 107.4, 121.5, 122.9, 123.3, 124.9, 128.3, 128.5, 129.3, 129.5, 132.2, 132.4, 146.3, 152.5, 160.4, 161.8, 162.2,165.9; Anal. calcd for $C_{24}H_{20}Br_2N_4O_3$(569.99): C, 50.37; H, 3.52; N, 9.79.

*Synthesis of 6-bromo-3-(6-(2-methoxyphenyl)-2-(morpholinomethylamino) pyrimidin-4-yl)-2H-chromen-2-one (**6gM**)*

It was obtained by reacting **(5g)** with morpholine and formaldehyde. m. p.: 177–179°C; Rf. value (benzene:acetone; 9:1): 0.67; IR (KBr, cm^{-1}): 3282.50 (N–H), 1707.60 (C=O), 1604.25 (C=N), 1544.30 (C=C), 1132.50 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 4.10(s, 1H, NH), 2.36(t, 4H, 2 × CH_2), 3.66 (t, 4H, 2 × CH_2), 6.84–7.71 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 51.3, 56.2, 66.7, 72.6, 107.4, 121.5, 121.7, 122.8, 124.9, 128.6, 129.3, 129.5, 146.3, 152.5, 157.6, 160.4, 161.8, 162.2, 165.9; MS *m/z*: 523.1, 237.0 (100%), 221.1, 205.1, 193.1; Anal. calcd for $C_{25}H_{23}BrN_4O_4$(522.09): C, 57.37; H, 4.43; N, 10.70.

*Synthesis of 6-bromo-3-(6-(3-methoxyphenyl)-2-(morpholinomethylamino) pyrimidin-4-yl)-2H-chromen-2-one (**6hM**)*

It was obtained by reacting **(5h)** with morpholine and formaldehyde. m. p.: 173–175°C; Rf. value (benzene:acetone; 9:1): 0.65; IR (KBr, cm^{-1}) : 3285.20 (N–H), 1708.60 (C=O), 1603.30 (C=N), 1542.60 (C=C), 1129.60 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 4.09 (s, 1H, NH), 2.35(t, 4H, 2 × CH_2), 3.65(t, 4H, 2 × CH_2), 6.84–7.71 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 51.3, 55.8, 66.7, 72.5, 107.4, 111.5, 114.5, 119.9, 121.5, 122.9, 124.9, 128.6, 129.2, 129.5, 130.5, 134.3, 146.2, 152.5, 160.4, 161.8, 162.2, 165.9; Anal. calcd for $C_{25}H_{23}BrN_4O_4$(522.09): C, 57.37; H, 4.43; N, 10.70.

*Synthesis of 6-bromo-3-(6-(2,4-dichlorophenyl)-2-(morpholinomethylamino) pyrimidin-4-yl)-2H-chromen-2-one (**6iM**)*

It was obtained by reacting **(5i)** with morpholine and formaldehyde. m. p.: 175–177°C; Rf. value (benzene:acetone; 9:1): 0.71; IR (KBr, cm^{-1}): 3280.10 (N–H), 1705.50 (C=O), 1605.80 (C=N), 1540.95 (C=C), 1133.45 (C–O–C); ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 4.08 (s, 1H, NH), 2.36 (t, 4H, 2 × CH_2), 3.65 (t, 4H, 2 × CH_2), 6.85–7.73 (m, 8H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm) : 51.2, 66.7, 72.5, 107.4, 121.5, 122.8, 124.9, 127.6, 128.3, 128.5, 129.2, 129.5, 130.5, 130.8, 133.7, 135.8, 146.3, 152.5, 157.6, 160.4, 161.8, 162.2, 165.9; MS *m/z*: 338, 301.0, 196.11, 100.2(100%); Anal. calcd for $C_{24}H_{19}BrCl_2N_4O_3$(560): C, 51.27; H, 4.21; N, 9.96.

*Synthesis of 7-bromo-3-(6-(2, 6-dichlorophenyl)-2-(morpholinomethylamino) pyrimidin-4-yl)-2H-chromen-2-one (**6jM**)*

It was obtained by reacting **(5j)** with morpholine and formaldehyde. m. p.: 171–173°C; Rf. value (benzene:acetone; 9:1): 0.66; IR (KBr, cm^{-1}): 3287.20 (N–H), 1705.80 (C=O), 1610.16 (C=N), 1543.50 (C=C), 1132.40 (C–O–C);^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 4.04 (s, 1H, NH), 2.35 (t, 4H, 2 × CH_2), 3.65(t, 4H, 2 × CH_2), 6.84–7.73 (m, 8H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 51.2, 66.7, 72.5, 107.4, 121.5, 122.8, 124.9, 127.5, 127.6, 128.5, 129.3, 129.5, 131.7, 133.9, 146.3, 152.5, 157.6, 160.4, 162.2, 165.9; Anal.calcd for $C_{24}H_{19}BrCl_2N_4O_3$(560): C, 51.27; H, 4.21; N, 9.96.

*Synthesis of 3-(2-((piperidin-1-yl) methylamino)-6-(substituted)pyrimidin-4-yl)-6-bromo-2H-chromen-2-one Compounds (**6aP–6jP**)*

Conventional method A mixture of compounds **(5a–5j)** (0.01 mol) and piperidine (0.01 mol) and formaldehyde (0.02) was refluxed in ethanol for 6–10 h. The reaction mixture was reduced to half of it's volume and poured on crushed ice. The product so obtained was washed with water repeatedly, dried, and recrystallized from ethanol. The formation of compounds (**6aP–6jP**) can be explained on the basis of "Mannich reaction".

Microwave method

A mixture of compounds **(5a–5j)** (0.01 mol) and Piperidine (0.01 mol) and formaldehyde (0.02) were taken in a conical flask, covered with a glass funnel. A petridish containing few ice cubes was kept on funnel to prevent excess evaporation of solvent. The reaction mixture was exposed to microwave irradiation for 5 min at 480 W. A beaker containing water was also kept in oven to serve as a heat sink, to monitor the progress of reaction, a TLC was run after every minute of microwave irradiation using "Benzene:Acetone" (9:1) solvent system. After completion of reaction, the solution mixture was concentrated and poured on to crushed ice. The compound so obtained were filtered at pump, dried, and recrystallized from ethanol to get pure crystalline solid.

*Synthesis of 3-(2-((piperidin-1-yl) methylamino)-6-(2-chlorophenyl)pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (**6aP**)*

It was obtained by reacting **(5a)** with piperidine and formaldehyde. m. p.: 168–170°C; Rf. value (benzene:acetone; 9:1): 0.72; IR (KBr, cm^{-1}): 3278.15 (N–H), 1708.06 (C=O), 1607.25 (C=N), 1542.55 (C=C), 1132.40 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 4.11 (s, 1H, NH), 4.16 (s, 2H, CH_2), 1.52 (m, 6H, 3 × CH_2), 2.28 (t, 4H, 2 × CH_2), 6.82–7.55 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 25.6, 25.9, 52.11, 72.5, 108.1, 121.4, 122.5, 124.9, 127.5, 128.6, 129.1, 129.3, 129.5, 129.6, 129.8, 130.1, 130.4, 132.1, 152.5, 160.4, 161.8, 162.3, 165.3; MS *m/z*: 526.3, 301.0, 285.0, 281.0 (100%), 267.1, 208.2,163.0; Anal. calcd for $C_{25}H_{22}BrClN_4O_2$ (526.06): C, 57.10; H, 4.22; N, 10.66.

*Synthesis of 3-(2-((piperidin-1-yl) methylamino)-6-(3-chlorophenyl)pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (**6bP**)*

It was obtained by reacting **(5b)** with piperidine and formaldehyde. m. p.: 170–172°C; Rf. value (benzene:acetone; 9:1): 0.73; IR (KBr, cm^{-1}): 3279.20 (N–H), 1707.10 (C=O), 1608.30 (C=N), 1542.85(C=C), 1132.80 (C–O–C); ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 4.12 (s, 1H, NH), 1.53 (m, 6H, 3 × CH_2), 2.27 (t, 4H, 2 × CH_2), 6.85–7.73 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 25.7, 25.6, 26.1, 52.0, 52.1, 72.6, 107.5, 121.5, 122.6, 124.9, 125.9, 128.5, 129.2, 129.4, 130.8, 134.6, 134.9, 146.2, 152.3, 160.4, 161.1, 162.1, 165.9; Anal. calcd for $C_{25}H_{22}BrClN_4O_2$ (526.06): C, 57.10; H, 4.22; N, 10.66.

*Synthesis of 3-(2-((piperidin-1-yl)methylamino)-6-(4-chlorophenyl)pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (**6cP**)*

It was obtained by reacting **(5c)** with piperidine and formaldehyde. m. p.: 176–178°C; Rf. value (benzene:acetone; 9:1): 0.66; IR (KBr, cm^{-1}): 3276.80 (N–H), 1705.70 (C=O), 1610.20 (C=N), 1544.32 (C=C), 1131.50 (C–O–C); ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 4.10 (s, 1H, NH), 1.51 (m, 6H, 3 × CH_2), 2.26 (t, 4H, 2 × CH_2), 6.86–7.74 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 25.8, 25.9, 52.2, 72.7, 107.4, 122.8, 124.9, 128.6, 129.2, 129.5, 131.4, 134.5, 146.2, 152.6, 160.4, 161.9, 162.2, 165.9; Anal. calcd for $C_{25}H_{22}BrClN_4O_2$ (525.82): C, 57.14; H, 4.24; N, 10.69.

*Synthesis of 3-(2-((piperidin-1-yl) methylamino)-6-(2-bromophenyl)pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (**6dP**)*

It was obtained by reacting **(5d)** with piperidine and formaldehyde. m. p.: 172–174°C; Rf. value (benzene:acetone; 9:1): 0.73; IR (KBr, cm^{-1}): 3279.15 (N–H), 1707.26 (C=O), 1608.35 (C=N), 1541.50 (C=C), 1130.49 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 4.12 (s, 1H, NH), 1.52 (m, 6H, 3 × CH_2), 2.25 (t, 4H, 2 × CH_2), 6.87–7.73 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 25.7, 25.1,

52.1, 72.6, 107.4, 120.4, 121.5, 122.8, 124.7, 128.2, 128.6, 129.1, 129.6, 131.2, 132.4, 139.9, 146.3, 152.5, 160.3, 161.8, 162.1, 165.7; MS *m/z*: 570.9, 428.8, 275.0, 268.0, 258.9; Anal. calcd for $C_{24}H_{22}Br_2N_4O_2$ (570.01): C, 52.65; H, 3.89; N, 9.82.

*Synthesis of 3-(2-((piperidin-1-yl) methylamino)-6-(3-bromophenyl) pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (**6eP**)*

It was obtained by reacting **(5e)** with piperidine and formaldehyde. m. p.: 175–178°C; Rf. value (benzene:acetone; 9:1): 0.72; IR (KBr, cm^{-1}): 3278.85 (N–H), 1708.86 (C=O), 1606.30 (C=N), 1543.15 (C=C), 1130.90 (C–O–C); ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 4.11 (s, 1H, NH), 1.53 (m, 6H, 3 × CH_2), 2.25 (t, 4H, 2 × CH_2), 6.85–7.74 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 25.7, 25.8, 52.2, 72.5, 107.3, 121.4, 122.6, 124.9, 126.6, 128.5, 129.5, 131.6, 131.8, 133.2, 135.5, 146.2, 152.6, 160.4, 161.9, 162.3, 165.8; Anal.calcd for $C_{25}H_{22}Br_2N_4O_2$ (570.01): C, 52.65; H, 3.89; N, 9.82.

*Synthesis of 3-(2-((piperidin-1-yl) methylamino)-6-(4-bromophenyl) pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (**6fP**)*

It was obtained by reacting **(5f)** with piperidine and formaldehyde. m. p.: 178–180°C; Rf. value (benzene:acetone; 9:1): 0.68; IR (KBr, cm^{-1}): 3280.15 (N–H), 1708.60 (C=O), 1606.85 (C=N), 1542.35 (C=C), 1132.60 (C–O–C); ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 4.08 (s, 1H, NH), 1.51 (m, 6H, 3 × CH_2), 2.26 (t, 4H, 2 × CH_2), 6.89–7.76 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 25.7, 25.8, 52.1, 72.6, 107.4, 121.5, 122.9, 123.3, 124.9, 128.6, 129.2, 129.5, 129.5, 129.8, 132.2, 132.4, 146.2, 152.5, 160.4, 161.8, 162.2, 165.7; Anal.calcd for $C_{25}H_{22}Br_2N_4O_2$ (570.01): C, 52.65; H, 3.89; N, 9.82.

*Synthesis of 3-(2-((piperidin-1-yl) methylamino)-6-(2-methoxyphenyl) pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (**6gP**)*

It was obtained by reacting **(5g)** with piperidine and formaldehyde. m. p.: 177–179°C; Rf. value (benzene:acetone; 9:1): 0.67; IR (KBr, cm^{-1}): 3276.95 (N–H), 1708.45 (C=O), 1609.25 (C=N), 1543.55 (C=C), 1132.42 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 4.09 (s, 1H, NH), 1.52 (m, 6H, 3 × CH_2), 2.25 (t, 4H, 2 × CH_2), 6.87–7.75 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6,δ,ppm): 25.7, 25.8, 52.2, 56.4, 72.5, 107.3, 114.9, 119.3, 121.4, 121.7, 122.8, 124.9, 128.6, 128.7, 129.2, 129.6, 129.9, 146.2, 152.6, 157.6, 160.4, 161.8, 165.9; MS *m/z*: 521.0, 408.0, 267.1, 226.9 (100%), 209.1; Anal. calcd for $C_{26}H_{25}BrN_4O_3$ (521.41): C, 59.89; H, 4.89; N, 10.75.

*Synthesis of 3-(2-((piperidin-1-yl) methylamino)-6-(3-methoxyphenyl) pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (**6hP**)*

It was obtained by reacting **(5h)** with piperidine and formaldehyde. m. p.: 173–175°C; Rf. value (benzene:acetone; 9:1): 0.65; IR (KBr, cm^{-1}): 3278.90 (N–H), 1709.08 (C=O), 1607.30 (C=N), 1542.95 (C=C), 1131.40 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 4.10 (s, 1H, NH), 1.53 (m, 6H, 3 × CH_2), 2.26 (t, 4H, 2 × CH_2), 6.88–7.7 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6,δ,ppm): 25.7, 25.8, 52.8, 55.8, 72.5, 107.5, 114.5, 119.7, 121.5, 122.8, 124.9, 128.5, 129.2, 129.6, 130.4, 134.2, 146.2, 152.6, 160.4, 161.3, 162.2, 165.9; Anal.calcd for $C_{26}H_{25}BrN_4O_3$ (521.41): C, 59.92; H, 4.85; N, 10.77.

*Synthesis of3-(2-((piperidin-1-yl) methylamino)-6-(2,4-dichlorophenyl)pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (**6ip**)*

It was obtained by reacting **(5i)** with piperidine and formaldehyde. m. p.: 179–171°C; Rf. value (benzene:acetone; 9:1): 0.71; IR (KBr, cm^{-1}): 3280.10 (N–H), 1705.50 (C=O), 1605.80 (C=N), 1540.95 (C=C), 1133.45 (C–O–C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 4.13 (s, 1H, NH), 1.53 (m, 6H, 3 × CH_2), 2.26 (t, 4H, 2 × CH_2), 6.82–7.74 (m, 8H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6,δ, ppm): 25.6, 25.8, 52.8, 72.5, 107.4, 107.4, 121.3, 122.9, 124.9, 127.7, 128.3, 129.1, 129.5, 130.7, 133.6, 135.9, 152.5, 162.3, 161.7, 165.9; MS *m/z*: 558.0, 510.9, 326.1 (100%), 208.1, 149.1; Anal.calcd for $C_{25}H_{21}BrCl_2N_4O_2$ (521.41): C, 53.59; H, 3.78; N, 10.00.

*Synthesis of 3-(2-((piperidin-1-yl) methylamino)-6-(2,6-dichlorophenyl) pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (**6jP**)*

It was obtained by reacting **(5j)** with piperidine and formaldehyde. m. p.: 187–189°C; Rf. value (benzene:acetone; 9:1): 0.76; IR (KBr, cm^{-1}): 3277.95 (N–H), 1710.09 (C=O), 1610.25 (C=N), 1542.75 (C=C), 1132.24 (C–O–C);^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 4.21 (s, 1H, NH), 1.51 (m, 6H, 3 × CH_2), 2.21 (t, 4H, 2 × CH_2), 6.85–7.81 (m, 8H, Ar–H); ^{13}C NMR ($CDCl_3$-d_6, δ, ppm): 25.5, 25.7, 52.3, 72.6, 107.1, 121.3, 122.9, 124.9, 127.5, 127.5, 127.9, 128.6, 129.3, 133.6, 146.9, 152.1, 162.8, 161.7, 160.7, 165.5; Anal. calcd for $C_{25}H_{21}BrCl_2N_4O_2$ (521.41): C, 53.59; H, 3.78; N, 10.00.

Table 2 Analgesic activity of compounds (**6aP–6jP**, **6aM–6jM**) by acetic acid-induced writhing response model

Compounds tested	Percent protection		
	0.5 h	1 h	2 h
Diclofenac sodium	95.87 ± 0.33	94.25 ± 0.31	84.53 ± 0.37
6aP	89.64 ± 0.61***	84.83 ± 0.47***	52.06 ± 0.76***
6bP	81.87 ± 0.48	83.25 ± 0.62	51.53 ± 0.21
6cP	83.94 ± 0.31	77.47 ± 0.95	61.86 ± 0.61
6dP	55.96 ± 0.98	40.31 ± 0.86	15.47 ± 1.23
6eP	41.97 ± 1.02**	37.70 ± 2.31	39.16 ± 1.96
6fP	49.74 ± 0.48	41.88 ± 0.67	32.47 ± 0.79
6gP	77.72 ± 0.48	65.44 ± 0.93	33.50 ± 0.61
6hP	74.09 ± 0.42	63.87 ± 0.85	35.05 ± 1.63
6iP	83.94 ± 0.48	69.12 ± 0.70	38.14 ± 1.69
6jP	26.43 ± 0.91	18.32 ± 0.58	15.47 ± 0.76
6aM	97.93 ± 0.21***	87.97 ± 0.60***	64.43 ± 1.28
6bM	69.95 ± 1.17	62.30 ± 0.93	40.71 ± 1.60
6cM	98.45 ± 0.22***	89.54 ± 0.61***	55.68 ± 1.33
6dM	59.59 ± 1.59	50.27 ± 1.25	47.94 ± 1.85
6eM	52.33 ± 0.88	45.55 ± 1.17	47.42 ± 2.00
6fM	61.66 ± 0.91	51.30 ± 1.02	46.89 ± 1.14
6gM	41.97 ± 1.02	36.13 ± 1.31	37.61 ± 0.95
6hM	60.62 ± 0.96	53.41 ± 0.95	47.42 ± 0.89
6iM	95.34 ± 0.43***	85.36 ± 0.56***	69.60 ± 1.30***
6jM	95.34 ± 0.43***	87.96 ± 0.48***	75.26 ± 0.37***

Method—acetic acid-induced writhing response model, test animals—albino mice, number of animals per group—6, route of administration—oral, standard—diclofenac sodium (20 mg/kg), $P \leq 0.001$ when compared to control. Statistical analysis the statistical analysis was performed by one-way ANOVA followed by Dunnet's test

Pharmacological screening

Animals

The in vivo analgesic activity done on Albino-Swiss mice weighing (20–25 g) and laboratory conditions maintained (24 ± 2°C; relative humidity 60–70%). The protocol was approved by the institutional animal ethics committee for the purpose of control and supervision on experiments on animals (IAEC, Approval No. 711/02/a/CPCSEA) before experiment. Albino-Swiss mice from laboratory animal house section, M.I.E.T., Meerut were used in the study. The animals were kept in polypropylene cages and maintained on balanced ration with free access to clean drinking water. All experimental procedures were conducted accordance with the guide for care and use of laboratory animals.

Analgesic activity (acetic acid-induced writhing response model)

The compounds were investigating their analgesic activity in acetic acid-induced writhing response in Swiss-albino mice by the method (Turner, 1965, Collier *et al.,* 1968). The mice were selected and divided into 22 groups (six in each group), starved for 16 h and pre-treated as follows, the first group which served as control positive was orally received distilled water in appropriate volumes. The second to eleventh groups were received the aqueous suspension of synthesized compounds (**6aP–6jP** and **6aM–6jM**) orally in a dose of 20 mg/kg. The last group was orally received Diclofenac sodium in a dose of 20 mg/kg. After 30 min, each mice were administered 1% of an aqueous solution of acetic acid (10 ml/kg) and the mice were then placed in transparent boxes for observation. The number of writhes was counted for 15 min after acetic acid injection at 0.5, 1, and 2 h (Table 2, Fig. 1). The number of writhes in each treated group was compared to that of a control group and that recorded by following ratio:

$$\% \text{ Protection} = \text{Control mean} - \text{treated mean}/\text{Control mean} \times 100$$

Acute-ulcerogenic activity

Acute-ulcerogenic test was done according to Cioli *et al.* (1979). Albino rats (150–200 g) were divided into different groups consisting of six animals in each group. Ulcerogenic activity was evaluated after p. o. administration of test compounds or standard drug at the dose of 60 mg/kg. Control rats received p. o. administration of

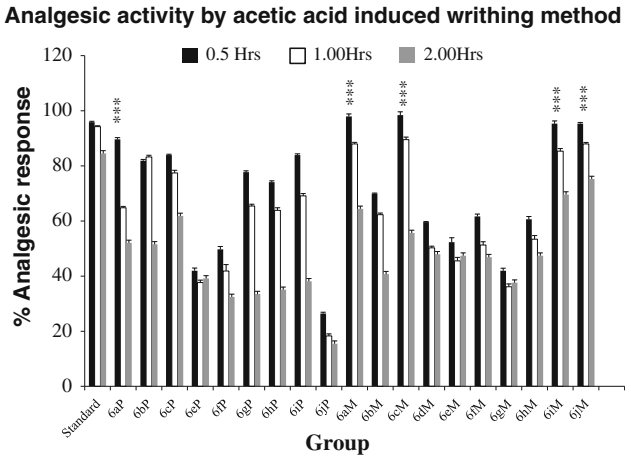


Fig. 1 Analgesic responses of synthesized compounds by acetic acid-induced writhing method. Values were expressed as mean ± SEM and $P \leq 0.001$ indicates the level of statistical significance as compared with control

Table 3 Ulcerogenic response of the various groups of compounds tested on the stomach of rats

S. no.	Groups	No. of ulcer spots
1.	Control group	2.67 ± 0.33
2.	**6aP**	13.67 ± 1.20***
3.	**6aM**	8.33 ± 0.88***
4.	**6cM**	7.00 ± 1.00***
5.	**6iM**	2.33 ± 0.33
6.	**6jM**	6.67 ± 1.20

Values are expressed as Mean ± SEM and *** $P \leq 0.001$ indicates the level of statistical significance as compared with control

vehicle (suspension of 1% methyl cellulose). Food but not water was removed 24 h before administration of the test compounds. After the drug treatment, the rats were fed normal diet for 17 h and then sacrificed. The stomach was removed and opened along the greater curvature, washed with distilled water and opened along the greater curvature, washed with distilled water, and cleaned gently by dipping in saline. The gastric mucosa of the rats was examined by means of a 4× binocular magnifier. The lesions were counted and reported in Table 3 and Fig. 2 see Scheme 1.

Determination of ulcerogenic activity by histological examination

A transverse section of the greater curvature of stomach was collected from formalin fixed stomach. Paraffin-embedded tissue sections were prepared at a thickness of 5 μm and stained with hematoxylin and eosin (H & E) for evaluation of cellular structure (Fig. 3). All histological

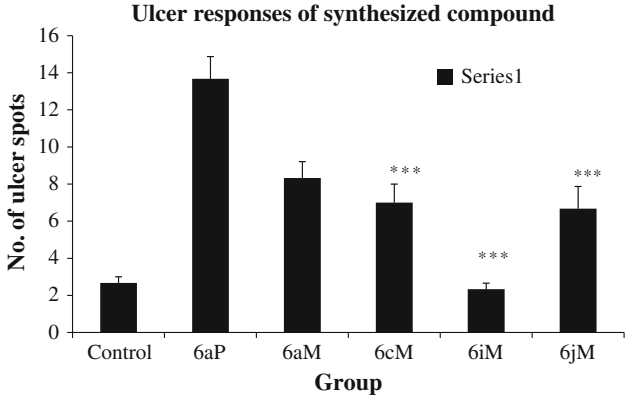


Fig. 2 Ulcerogenic responses of synthesized compounds. Values were expressed as mean ± SEM and ***$P \leq 0.001$ indicates the level of statistical significance as compared with control

examinations were performed by evaluating one stomach section per animal, using an Olympus microscope (Model BX 04).

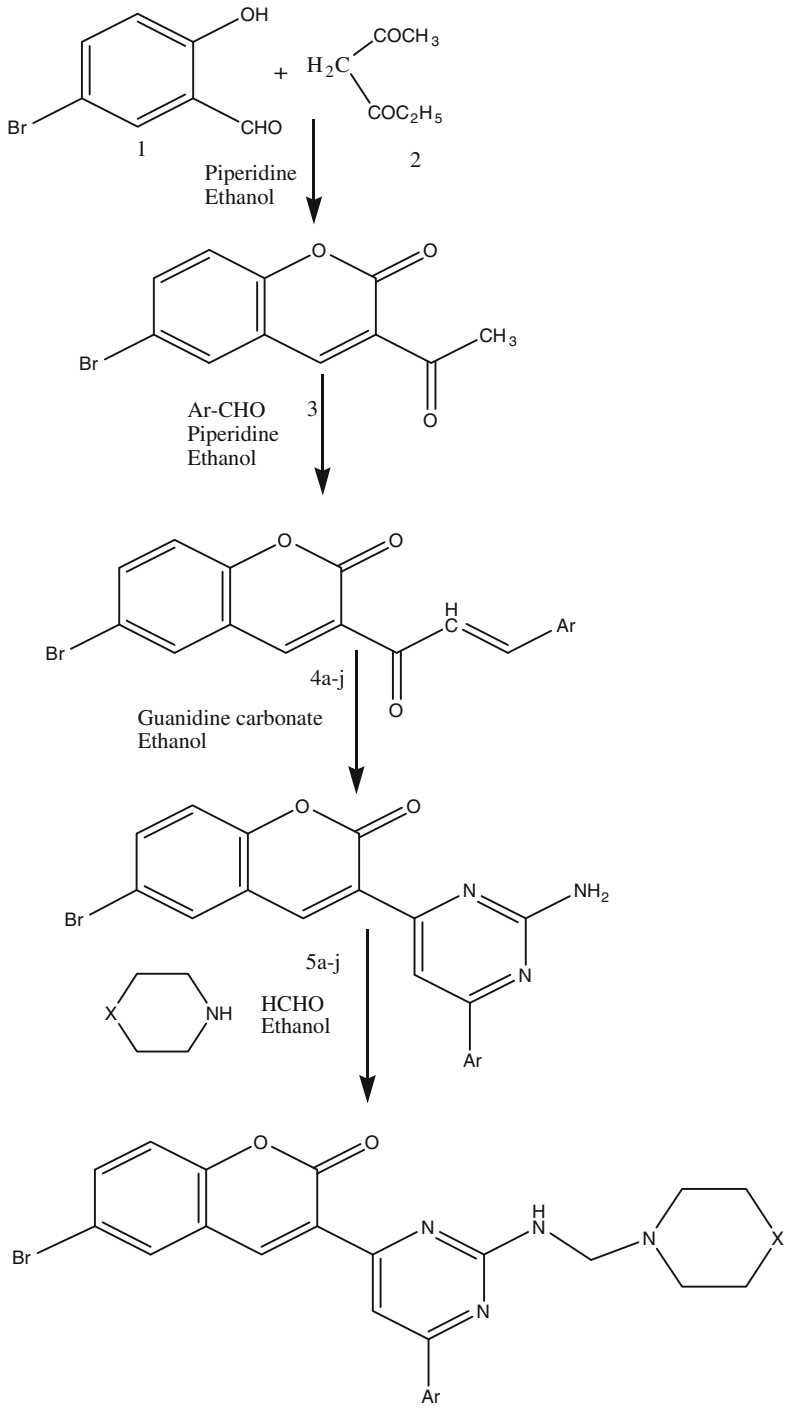
Statistical analysis

One-way analysis of variance (ANOVA) followed by Dunnet's *t* test for multiple comparisons of compounds in different pharmacological assays. Data are expressed as mean ± SEM.

Result and discussion

From these data a preliminary SAR can be drawn for synthesized compounds. A novel series of compounds (**6aP–6jP** and **6aM–6jM**) were synthesized and characterized. The synthesized compounds screened for their in vivo analgesic activity according to the method by Turner and Collier using Swiss albino mice. Some of the synthesized compounds viz., **6aP**, **6aM**, **6cM**, **6iM**, and **6jM** exhibited significant analgesic activity and compounds **6cM** and **6iM** have shown highly significant activity. The remaining compounds have shown less analgesic activity comparable to that of standard drug Diclofenac sodium in the acetic acid induced writhing response model (Fig. 1). All derivatives tested significantly suppressed the spontaneous locomotor activity of mice during a 30 min observation period. The most potent effects were produced by derivative, **6aP**, **6aM**, **6cM**, **6iM**, and **6jM**. On the contrary, the weakest activity in this test was displayed **6eP**, **6jP**, and **6gM**. The data for compounds, tested for analgesic activity, are presented in Fig. 1. From the data presented above, it follows that the most active substance in the acetic acid-induced writhing method is

Scheme 1 Schematic diagrams for the synthesis of pyrimidine derivatives **(6aM–6jM**, **6aP–6jP)**

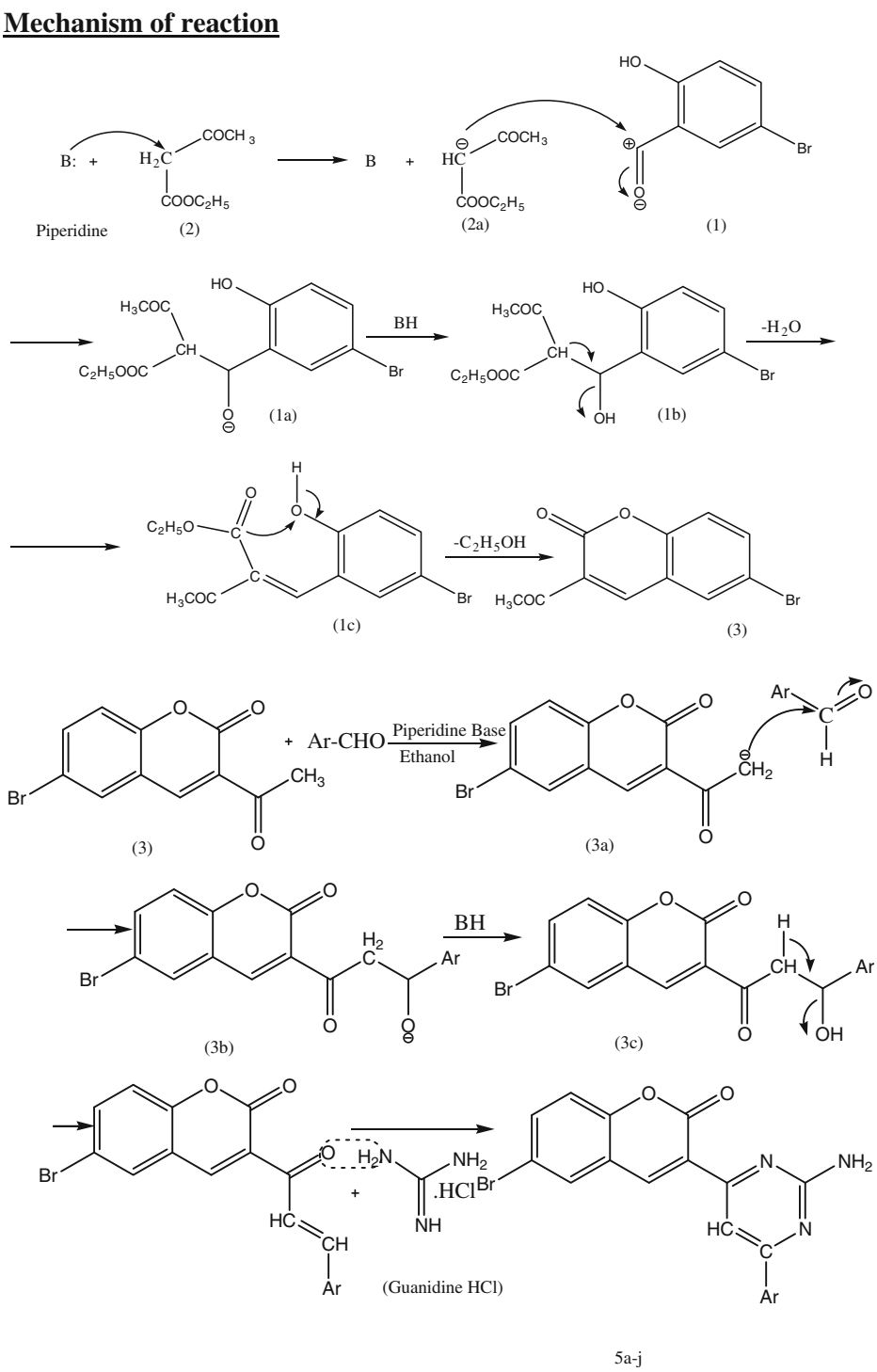


6aM-6jM, 6aP-6jP

Ar =o-Chloro Benzaldehyde, m-Chloro Benzaldehyde,p-Chloro Benzaldehyde
o -Bromo Benzaldehyde,m -BromoBenzaldehyde,p -BromoBenzaldehyde
o -Methoxy Benzaldehyde,m -Methoxy Benzaldehyde
2,4 dichloro Benzaldehyde
2,6-dichloro Benzaldehyde

X= CH_2, O

Scheme 1 continued

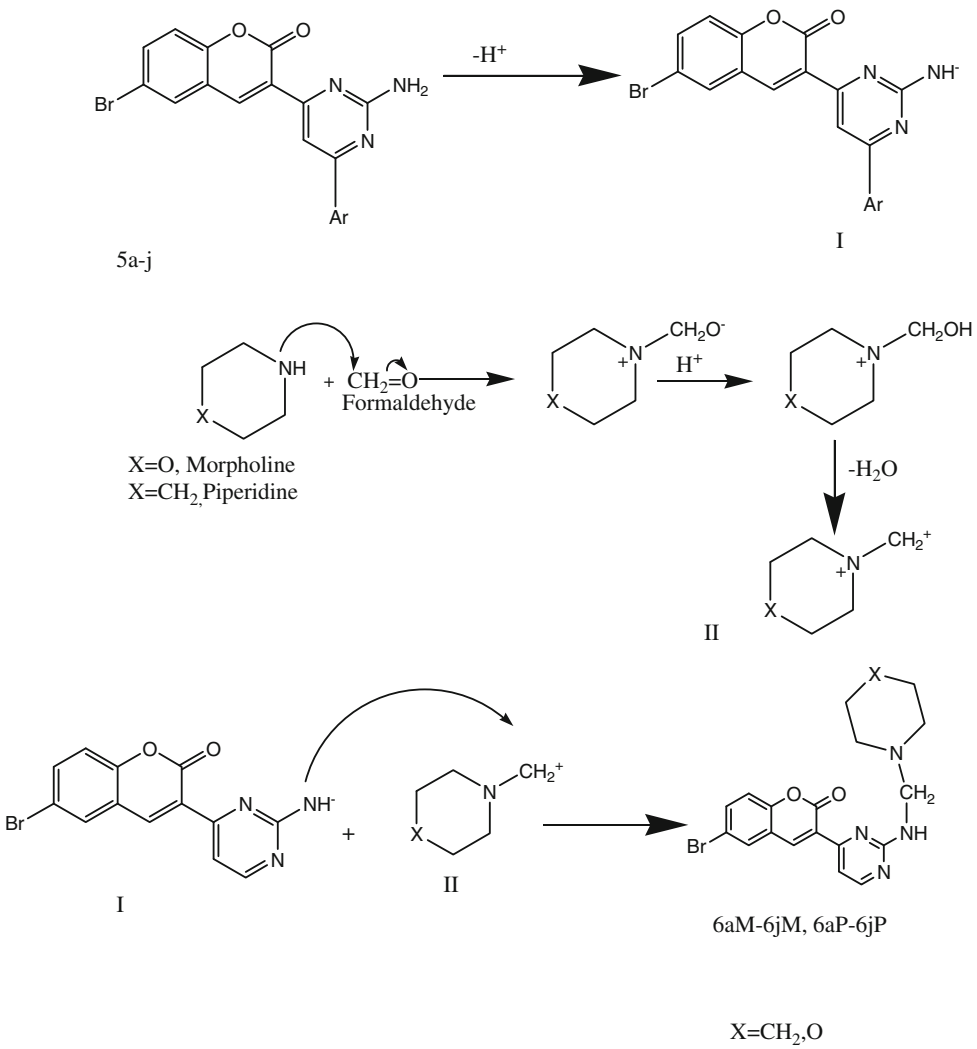


6-bromo-3-(6-(4-chlorophenyl)-2-(morpholinomethylamino)pyrimidin-4-yl)-2H-chromen-2-one (**6cM**). Modification of position of chlorine from 2 positions as in compound **6aM** to position 2, 4, and 6 as in compound **6iM**, **6jM** as well as some piperidine derivative-like **6aP** also produced the potent analgesic compound (Table 2; Fig. 1). The compounds which showed highly significant analgesic activity, i.e., compounds **6aP**, **6aM**, **6cM**, **6iM**, and **6jM** are further evaluated for ulcerogenic activity (Table 3; Figs. 2, 3).

Conclusion

Conventional as well as microwave synthesis play an important role in medicinal chemistry and drug discovery.

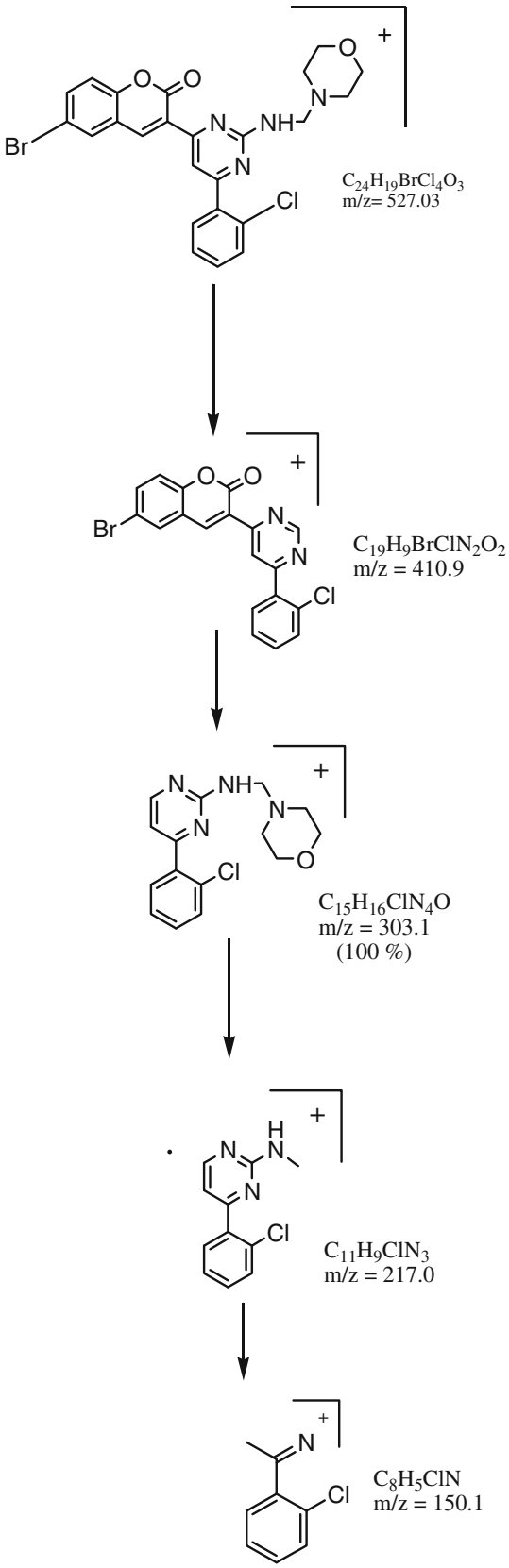
Scheme 1 continued



Microwave technique reduces reaction time from days or hour to minutes or even seconds. A new microwave procedure for the rapid and efficient synthesis of pyrimidine derivatives has been developed. During our studies the conventional synthesis of **6aM–6jM** and **6aP–6jP** required time 8–10 h and the % yield were often poor, hence application of microwave technique for the synthesis of the title compounds with an objective to reduce reaction time and increase % yield was explore. The microwave heating effectively reduced the reaction time from 8 to 10 h to a few minutes (2–8 min). A new series of compounds (**6aP–6jP** and **6aM–6jM**), i.e., pyrimidine analogs were synthesized by piperidine and morpholine and characterized. The synthesized compounds screened for their in vivo analgesic activity. Some of the synthesized compounds viz., **6aP**, **6aM**, **6cM**, **6iM**, and **6jM** exhibited significant analgesic activity and compounds **6cM**, **6iM**, and **6jM** have shown highly significant activity. The remaining compounds have shown less analgesic activity comparable to that of standard drug Diclofenac sodium in the acetic acid-induced writhing response model at 20 mg/kg body weights of the animals (Fig. 1). From all the tested compounds, five compounds, i.e., **6aP**, **6aM**, **6cM**, **6iM**, and **6jM** have been evaluated for ulcerogenic activity because of their efficient analgesic activity and compound **6iM** was found to be most promising analgesic agent which is devoid of ulcerogenic effects (Figs. 2, 3).

Scheme 1 continued

Mass fragmentation pattern of synthesized derivative



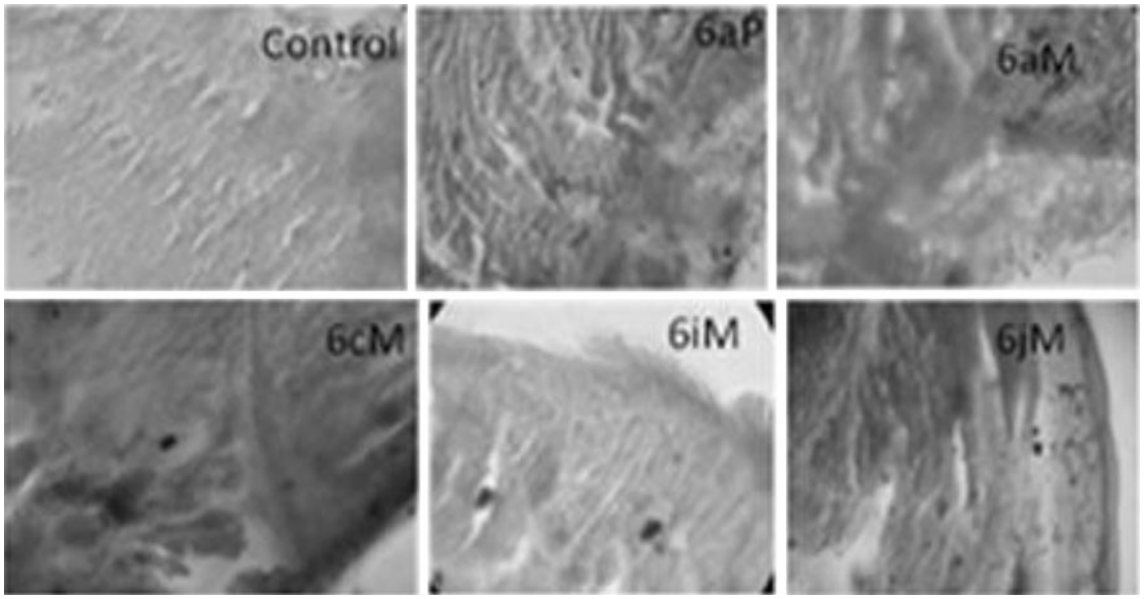


Fig. 3 Picture showing histopathological examination of the transverse section of the greater curvature of stomach part of rats. The study was conducted on the six groups of rats, i.e., Control, Compound **6aP**, Compound **6aM**, **6cM**, **6iM**, and Compound **6jM**. Control group (C): As it is clearly visible from the picture that there are very less or almost negligible ulcer spots in the transverse section of stomach of control group of rats. Compound **6aP** group: The picture is showing the ulcer spots. This group shows the significant difference from control group. Compound **6aM** group: The picture is showing the ulcer spots. This group shows the significant difference from control group. Compound **6cM** Group: The picture is showing the ulcer spots. This group shows the significant difference from control group Compound **6iM** group: The picture is showing very less number of ulcer spots. This group does not show the significant difference from control group. Compound **6jM** group: The picture is showing the ulcer spots. This group shows the significant difference from control group

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